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10/575,369	04/11/2006	Marco Alexander Van Den Berg	GRT/4662-168	9073

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,369	VAN DEN BERG, MARCO ALEXANDER	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-25,27 and 28* is/are pending in the application.

4a) Of the above claim(s) *10-21, 23-25 and 27-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed November 26, 2008 on March 26, 2009 is acknowledged.

Claim Disposition

2. Claims 27-28 have been added. Claims 1-21, 23-25 and 27-28 are pending. Claims 1-9 are under examination. Claims 10-21, 23-25 and 27-28 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claim Objection

3. Claims 1 and 8 are objected to because of the following informalities:

For clarity and precision of claim language, it is suggested that claim 1 is amended to read, "...to which a label is covalently coupled; and...".

For clarity and precision of claim language, it is suggested that claim 8 is amended to read, "...DNA, RNA or protein expression levels are altered...".

Correction is required.

Claim Rejections - 35 USC э 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is

claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966."Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents" of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers,* 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe,* 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents" of the University of California v. Eli Lilly & Co.,* 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The

MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli,* the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli,* 872, F.2d at 1012, 10 USPQ2d at 1618. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for *a prima facie* case is discussed below.

Further, to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: a) the scope of the invention; b) actual reduction to

practice; c) disclosure of drawings or structural chemical formulas; d) relevant identifying characteristics including complete structure, partial structure, physical and/or chemical properties, and structure/function correlation; e) method of making the claimed compounds; f) level of skill and knowledge in the art; and g) predictability in the art.

The claimed invention is directed to a method for preparation of a modified host cell comprising: transfecting a host cell with at least one polypeptide to which a label is covalently coupled; and isolating the transfected host cell, wherein said at least one polynucleotide permanently changes a metabolic property of the transfected host cell as compared to the non-transfected host cell; wherein the label provides to the host cell a non-inheritable trait. The claimed invention is drawn to a genus of host cells, a genus of nucleotides, a genus of labels and a genus of metabolic property; not adequately described (see claim 1 for example). The instant specification describes the pGBDEL4L plasmid that is transfected in the host cell and the use of fluorescein as a label. However, the claimed invention comprises an unlimited amount of labels, detection means and host cells bearing the nucleic acid of interest. The cited prior art by Wolfe (set forth below) teach a DNA with a fluorescent label transfected in a host cell which falls within the scope of the claims as no specific nucleic acid is claimed; therefore the genus encompassed in the claims is large and variable. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus.

A representative number of species means that the species which are adequately described are representative of the entire genus. The written description

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The examiner acknowledges that the claims are not drawn to organisms *per se*, but to methods of use thereof. In this case, the recited organism comprising a genus of genes is a critical and essential element of the claimed invention. However, this distinction would not appear to differentiate the standard for a product claim as compared to a method claim, which uses that product. According to MPEP 2163.A.I, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art". The Court addressed a similar argument in *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). The *Rochester* Court found this difference to be a "semantic distinction" and held that "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court

observed, '[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment.'" Accordingly, in the instant case, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Moreover, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

5. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabled for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988*). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of host cells, detection means, labels, polynucleotides and metabolic property. The instant specification describes the pGBDEL4L plasmid that is transfected in a host cell and the use of fluorescein as a label. It is also disclosed that detection means is FACS, however, the breath of the claims encompasses any possible gene, any label (not just fluorescent ones), any host cell, any metabolic property (not just improved metabolite production or altered

morphology/growth on a specific substrate as recited by the specification) and any detection means (not just the recited FACS). No correlation is made between the structure of the DNA and its function in the method. It is noted that claim 4 recites types of label, claim 5 recites a detection means and claim 9 recites types of host cells, however, these claims do not rectify the deficiency of the description of the polynucleotide or metabolic properties.

Due to the large quantity of experimentation necessary to generate the infinite number of variables encompassed in the claims a skilled artisan cannot practice the full scope of the claimed invention, based on the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

The claimed invention is rendered as unpredictable based on the lack of guidance and the large amount of unknown variables encompassed in the claims.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would

have to engage in undue experimentation to construct the variables of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of host cells, polynucleotides etc. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*.

Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolff et al. (U.S. Patent No. 6,262,252, July 17, 2001).

Wolff et al. teach a general method of covalently attaching a label to a target molecule using detectable fluorescent tags (see paragraph 4 and 15). Wolff et al. specifically teach a method for covalently attaching a fluorescent label to a nucleic acid (see claims 1-8 of the patent). Wolff et al. teach cells transfected with a DNA (see paragraph 227). In addition, Wolff et al. teach gene transfer (see paragraph 57). Wolff et al. teach means of isolation (see paragraphs 95, 105 and 107). Therefore, the limitations of the claims are met by the reference.

7. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (AAPS Pharmsci, 1999, cited on the IDS filed January 18, 2007).

Johnson et al. teach a method for monitoring transfer of DNA during transfection, said method involving labeling a plasmid DNA with fluorescein-12-dUTP, flow cytometric detection and sorting of the fluorescent transfected cells (see pages 1-6). Therefore, the limitations of the claims are met by the reference.

Response to Arguments

8. Applicant's comments have been considered in full, however, are not persuasive. Note that the art rejections of record remain. It is noted that applicants provided a copy of the Danko reference, however, a PTO-1449 form was not included. If applicants would like this reference to appear on the face of the patent a PTO-1449 needs to be filed.

With respect to the Wolff reference applicant state that Danko et al. teach the same DNA as the Wolff patent and found only temporary effects on gene expression. This argument is not persuasive as the Danko et al. reference does not refer to the disclosure in Wolff. Further, the instant specification discloses at paragraph [0047] and [0045] that [T]his example demonstrates that applying directly detectable signals (in this case fluorescein) covalently coupled to DNA as a means of selecting and sorting the desired, modified cells results in cells in which the polynucleotide of interest triggers permanent metabolic changes. The results shown in table 1 demonstrate that protoplasts can resist the pressure in the FACS. Due to some clumping of protoplasts high and low scatter populations were isolated (see table 1). Only, cells with high scatter gave amdS positive clones (see sample E, table 1), demonstrating integration of fluorescent labeled DNA. So, after growing on synthetic media these cells lost the non-inheritable fluorescein marker, but retained the gene of interest". Thus, it appears the modification in the cell is being attributed to the DNA with fluorescein. Note that the

cited Wolff reference also teach the use of fluorescein coupled to a plasmid, therefore the cell is inherently modified.

With regard to the Johnson reference applicant opines that gene transfer did not occur. The Johnson reference on page 2, second paragraph disclose that "this article describes a method for monitoring the kinetics of the transfer of exogenous DNA during transfection....this method could detect cells containing internalized DNA as early as 1 hour after transfection and provide the intracellular location of the transferred DNA" (page 2). It is also disclosed in the materials and methods, that "a plasmid was labeled with fluorescein-12-dUTP (using nick translation). Thus both references are pertinent to the claimed invention, therefore, the rejections remain.

Note that two new grounds of rejections have been instituted under 35 USC 112 first paragraph for the reasons stated above.

Conclusion

9. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to HOPE A. ROBINSON whose telephone number is (571)272-0957. The examiner can normally be reached on Monday-Friday 9:00-6:30 from 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652